REMARKS

The Office Action mailed October 21, 2002, has been received and its contents carefully noted. The pending claims were claims 16-42 and 45-65. Claims 46-59 and 63-64 were rejected. Claims 16-42, 45, 60-62, and 65 were withdrawn from consideration. By this amendment, claims 16-42 and 45-65 have been cancelled, and claims 66-83 have been added. Support may be found in the specification and claims as originally filed. No statutory new matter has been added. Reconsideration is respectfully requested.

Claim Amendments

Applicants note that the new claims correspond to the former claims as follows:

1. New claims 66-79 correspond to former claims 46-59, respectively.
2. New claim 80 corresponds to former claim 63.
3. New claims 81-83 are newly proposed. Applicants submit new claims 66-68 on specific embodiments for representation of peptide sequences from Borrelia burgdorferi.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 46-59 and 63-64 under 35 U.S.C. 112, first paragraph because the Examiner deemed that the specification, while being enabling for the antigenic peptide sequence of Borrelia burgdorferi and iminodiacetic acid as the bridging group, the specification does not reasonably provide enablement for any type of ligand presenting assembly containing any peptide chain or its homologs or mimics, with any achiral di or tri or tetra carboxylic acid as a bridging group and any type of chemical moiety, target or marker group that elicits an

immune response under any given conditions of synthesis. The Examiner deemed that Applicants' broad steps of synthesis using any achiral dicarboxylic acid is nothing more than an invitation to experiment in the hope that a discovery can be made. The Examiner further stated that the specification does not teach any tri or tetracarboxylic acid as employed in the instant method.

Applicants submit that claims 46-50 have further been restricted to involve achiral dicarboxylic acids only. This means also that claim 49 has been restricted to the elected species imino acetic acid, and that claim 50 has been restricted to the dicarboxylic acids, the use of most of them being illustrated in the examples.

Applicants respectfully submit that the claims as presented are substantially limited to the use of simple achiral dicarboxylic acids as the bridging group (claims 66 and 68-70). The general applicability of these acids is illustrated with imino diacetic acid (Examples 1, 2 and 6), 3-amino glutaric acid (Examples 3, 4 and 5), glutaric acid (Examples 7, 9. 10 and 11) and tricarballylic acid (Example 8). Please note that although tricarballylic acid is in fact a tricarboxylic acid, it is used as a dicarboxylic acid, see e.g. Example 8, wherein the surplus carboxy group is available for subsequent coupling.

Furthermore, Applicants submit that the general applicability of the method of the invention for preparing LPA for presentation of peptide sequences has been illustrated for a wide number of sequences from different sources, for example, Borrelia burgdorferi (Examples 1-5), Mycobacterium tuberculosis (Examples 5-6), Chlamydia trachomatis (Examples 7-8 and Chlostridium thermosacchrolyticum (Example 12), as well as sequences derived from angiotensin-I (Examples 9-12).

Applicants also submit herewith a journal article, Roberts, D.M., *et al.* (2002) "Environmental regulation and differential production of members of the Bdr protein family of Borrelia burgdorferi" Infect. Immun. 70:7033-7041, which provides that experiments that allow the synthesis of five further peptide sequences from Borrelia burgdorferi. See p. 7034, right column, beginning at line 6, and Table 2.

Accordingly, no undue experimentation is necessary and only routine synthetic methods known in the art are necessary. Therefore, Applicants respectfully submit that the claims as pending are enabled and the rejection under 35 U.S.C. 112, first paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 46-65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner deemed that:

1. Claim 46 is incomplete for omitting essential steps, such omission amounting to a gap between the steps and that claim 47 step (c') is unclear since claim 6 step c does not recite that the dicarboxylic acid is protected at its N-terminus.

2. Claim 52 is inconsistent and broadens the base claim 46. The base claim does not recite for an additional chemical entity at the N-terminus of the achiral carboxylic acid and recites an N-protected group. The metes and bounds of the chemical entity, target and market, within the claimed context, are indefinite.

3. Claim 53 is indefinite for reciting the phrase "such as" because it is unclear whether the limitations following the phrase are part of the claimed invention.

4. Claim 54 is unclear as to the metes and bounds of the B or C epitopes of the peptide sequences, the combination of these epitopes or mimics thereof and furthermore it is not clear within the claimed context, "mimics" thereof i.e., in what context the peptide sequences is considered a mimic.

5. Claim 55 is unclear as to the basis by which a peptide sequence is considered to be "important" for an immune response.

6. Claims 56 and 57 are indefinite as the metes and bound of the homologous sequence are unclear especially since it is uncertain whether, in fact said sequence is "capable of reacting with the antibodies or provoking an immune response". Furthermore, it is not clear how a peptide sequence is derived from the OspC protein.

7. Claim 57 is indefinite in the recitation of LPA since claim 56 recites peptide sequences. Furthermore the language "C-terminal presentation of the C-terminal sequence" is confusing.

8. Claim 59 is confusing in its language especially since claim 56 does not recite LPA but peptide sequence.

9. Claim 64 is a duplicate of claim 58.

Applicants respectfully submit that the phrase "being attached" in claim 66, step (a), is not unclear, since it is commonly known in the art that during a solid phase synthesis the construct is temporarily attached to the solid phase, and, in the present claim it is stated that the construct is cleaved from the solid phase in step (d). The description also provides sufficient information for a person skilled in the art to

understand the scope and meaning of the claim. Accordingly, the phrase "during the synthesis" is in fact superfluous.

Applicants respectfully submit that the claims as amended obviate the remaining rejections under 35 U.S.C. 112, second paragraph. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. § 102(a)

The Examiner rejected claims 46-51 under 35 U.S.C. 102(a) as being anticipated by Lange et al. (J Pept. Sci.) or 35 U.S.C. 102(b) by Gilon et al. (Pept. Chem., Proc. Jpn. Symp.) for reasons advanced in the last Office Action. Specifically, the Examiner deemed the claims did not differentiate an intra from intermolecular cyclization and that there is nothing in the broad claimed method steps that lead to an intermolecular cyclization of the product.

Applicants respectfully submit that the present claims have been limited to a construct having a ring structure comprising the carboxylic acid and two ligands comprising the peptide sequences, viz. and intermolecular cyclization. Furthermore, the scope of the claimed dicarboxylic acids has been restricted to simple acids.

As neither Lange et al. nor Gilon et al. teach or suggest a construct having a ring structure comprising the carboxylic acid and two ligands comprising the peptide sequences, the present invention as claimed is novel and the rejection under 35 U.S.C. 102(a) should properly be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 56-59 and 63-64 under 35 U.S.C. 103(a) as being unpatentable over Mathiesen and Tomalia et al. in view of Gilon et al. or Lange et al. Specifically, the

Examiner deemed that the Applicants' arguments were not commensurate in scope with at least the broad claim 46.

Applicants respectfully submit that Mathiesen discloses a method of making a peptide from a sequence of OspC of Borrelia burgdorferi. Tomalia also discloses a method of making a peptide. However, as the Examiner admits in the Office Action dated 18 July 2001, none of these references teach the cyclization of the peptide.

Applicants submit that Gilon et al. discloses backbone cyclization involving the formation of lactam rings, viz. a totally different ring structure than the one used in the present application as claimed. This substantial difference between the present invention and the prior art is clearly expressed in the present claims. Nowhere does Gilon et al. teach or suggest making or using the ring structure of the presently claimed invention, a ring structure comprising carboxylic acid and two ligands comprising the peptide sequences. As lactam rings are different from the ring structures of the present invention, one of ordinary skill in the art would not be motivated to make the peptides of Mathiesen and Tomalia et al. into ring structures using the cyclization method of Gilon et al. with a reasonable likelihood of success in obtaining the ring structure of the present invention, comprising carboxylic acid and two ligands comprising the peptide sequences. Therefore, the combination of Mathiesen and Tomalia et al. and Gilon et al. do not render obvious the present invention as claimed and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Applicants further submit that the scope of the work disclosed by Lange et al. is synthesis and activity of dimeric bradykinin antagonists containing diamino dicarboxylic acid

bridge residues. This type of compound and the scope of the problem to be solved are decisively different from the compounds and the scope of the present invention. Therefore, Applicants respectfully submit that the Lange et al. is not properly a prior art reference. See *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). As Lange et al. cannot be used to establish a prima facie case of obviousness, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Even if Lange et al. is a proper prior art reference in connection with the present invention, according to Alberts et al., the bridging technique with half equivalent 2,7-bis(Boc-amino) suberic acid coupled to one equivalent of lysine (2Cl-Z-protected) attached to the synthesis resin appears slow and takes place over up to 4 days. See Alberts et al. p. 368, first paragraph. Applicants submit the reason for this slow reaction is not known, but for a person skilled in the art of peptide synthesis these facts clearly point away from employing general bridging technique. However, the prejudice that the bridging reaction should be a difficult reaction as such is probably based on a misinterpretation of the necessary conditions for the reaction. Since only half an equivalent can be used in a simple bridging reaction, the rate of reaction decreases as the reaction progresses and will at the end of the reaction be slow because of the very low concentration of the reacting dicarboxylic acid. Thus, it is necessary to couple for about 12 hours to achieve completion of the coupling reaction, which is in contrast to most SPPS (solid phase peptide synthesis), where reactions may be completed within a short time, e.g. 30 minutes, because an excess of reagent can be used.

Applicants submit in contrast to what might be expected from the reports by Lange et al. and by Alberts et al., the Applicants have surprisingly found no problems bridging

peptide chains longer than four amino acid residues. This is demonstrated in the examples with different dicarboxylic acids and with examples of peptide chains with different composition and of different length. Thus, imino diacetic acid (Examples 1, 2 and 6) and 3-amino-glutaric acid (Examples 3, 4 and 5) are used together with a 10-mer peptide, a 17-mer peptide and a 20-mer peptide, glutaric acid and tricarballylic acid with 15-mer peptides including non-natural amino acids (Examples 7 and 8), and 3-amino-glutaric acid with a 10-mer peptide (Examples 9, 10 and 11). In the 2002 article referred to above, the synthesis of further sequences with long chains are exemplified. All examples proceed with high bridging efficiency. These unexpected results differ significantly from that of the prior art.

As the method of the present invention unexpectedly allows the bridging of peptide chains longer than four amino acid residues, the present invention is nonobvious and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Request for Interview

Applicants respectfully request either a telephonic or an in-person interview should there be any remaining issues.

Extension of Time

A Petition for an Extension of Time for two (2) months under 37 C.F.R 1.136 and the appropriate fee are submitted herewith to extend the time for responding to the Office Action to March 21, 2003.

Conclusion

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and to allow the present claims in order to find this application to be in allowable condition.

Respectfully submitted,

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